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Compound A + B
↑ ↑
vit D. corticosteroid.

=) inv. ° ≠ to.

Nouveauté

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(54) Title: COMPOSITION FOR THE TREATMENT OF PSORIASIS COMPRISING A SILICONE AGENT, A CORTICOSTEROID AND VITAMIN D OR A DERIVATIVE THEREOF

(57) Abstract: The present invention relates to a stable anhydrous pharmaceutical composition comprising a silicone agent comprising at least one organopolysiloxane elastomer and as active principles vitamin D or a vitamin D derivative and a corticosteroid, to the process for preparing it and to its use for the topical treatment of psoriasis and other skin disorders.

COMPOSITION FOR THE TREATMENT OF PSORIASIS COMPRISING A SILICONE AGENT, A CORTICOSTEROID AND VITAMIN D OR A DERIVATIVE THEREOF

The present invention pertains to the field of the formulation of active principles for the purpose of topical pharmaceutical application.

The present invention relates more particularly to a stable anhydrous pharmaceutical composition comprising a silicone agent and as active principles vitamin D or a vitamin D derivative and a corticosteroid, to the process for preparing it and to its use for the topical treatment of psoriasis and other skin disorders.

Vitamin D and its derivatives are generally used in dermatology in the treatment of psoriasis since they limit the excessive production of cutaneous cells on the surfaces affected and possess proven advantages for the treatment of this ailment, which is characterized in particular by the presence of thick, squamous and dry lesions.

It is known that a certain number of active principles which exhibit advantageous therapeutic activity are sensitive to oxidation and in particular undergo chemical degradation leading to a substantial loss in their activity in the presence of water.

The combination in a single pharmaceutical composition of vitamin D or a vitamin D derivative with

a corticosteroid is not without its problems. This is because vitamin D or some vitamin D derivatives are unstable in an acidic environment (they have maximum stability at pH values of approximately 8) and certain corticosteroids are unstable in a basic environment (they exhibit maximum stability at a pH of approximately 4 to 6).

Consequently it is appropriate to formulate these active principles in anhydrous compositions.

The anhydrous compositions presently available on the market which allow the formulation of water-sensitive active principles while ensuring their effective chemical stability are generally ointment compositions. These ointment compositions are composed principally of petroleum jelly, mineral oil and/or vegetable oil. Some of the compositions comprising petroleum jelly, however, are felt after application to be sticky and greasy, and in addition are shiny. The greasy residue left on the skin prevents the patient afflicted by psoriasis from putting on his or her clothes again after treatment without the risk of leaving greasy marks thereon, which does not necessarily encourage the patient to follow his or her treatment. Non-compliance with the prescribed treatment is one of the main causes of failure; the article "*Patients with psoriasis and their compliance with medication, Richards et al., J. Am. Acad. Dermatol.,*

Oct. 1999, pp. 581-583" indicates that almost 40% of patients with a chronic disease such as psoriasis do not follow their treatment. The characteristics of the vehicle used in the pharmaceutical compositions are directly linked to the adherence by the patient to his or her treatment.

The ointment compositions presently on the market do not always lend themselves to the formulation of the active principle in a solubilized form.

EP 0 255 369 and US 6 103 250 describe formulations based for the most part on silicone derivatives, in which the water-sensitive active substances are formulated in a dispersed form. The dispersed form, however, is generally detrimental to optimum skin penetration and/or release of these active substances.

One of the aims of the present invention is to provide an anhydrous pharmaceutical composition intended for topical application that allows the abovementioned drawbacks to be removed.

Another aim of the present invention is to provide an anhydrous pharmaceutical composition intended for topical application wherein the active principles are in a solubilized form and exhibit prolonged stability.

The present invention accordingly provides an anhydrous pharmaceutical composition intended for the

treatment of psoriasis, characterized in that it comprises a silicone agent comprising at least one organopolysiloxane elastomer and, as active principles, a compound A selected from vitamin D or a vitamin D derivative and a compound B selected from a corticosteroid, the said compounds A and B each being in a solubilized form in the said composition.

By solubilized form is meant a dispersion in the molecular state in a liquid, no crystallization of the active being visible to the naked eye or even under an optical microscope with crossed polarization.

The composition of the invention is intended more particularly for topical application.

The active principles are in the solubilized state, thereby giving the compositions of the invention effective properties of release/skin penetration of each of the said active principles, in conjunction with more advantageous kinetics. The term "effective release/penetration capacity" refers to the effective distribution of the composition of the invention and hence of the active principles it comprises across the stratum corneum of the skin and also across the subcutaneous layers such as the epidermis and the dermis.

In particular the pharmaceutical composition according to the present invention is such that the difference in optimum pH stability of the compound A

and the optimum pH stability of the compound B is at least 1.

The term "anhydrous composition" refers for the purposes of the present invention to a composition which is substantially free of water, which is to say that it has a water content of less than or equal to 5% by weight relative to the total weight of the composition, in particular less than or equal to 3%, and especially zero.

The active principles forming part of the compositions of the invention, namely vitamin D or a vitamin D derivative and a corticosteroid, possess a therapeutic activity against dermatological ailments or skin complaints such as, for example, psoriasis.

By vitamin D is meant the various forms of vitamin D such as, for example, vitamin D_1, D_2, D_3 or vitamin D_4.

By vitamin D derivatives are meant compounds which exhibit biological properties analogous to those of vitamin D, especially properties of transactivation of vitamin D response elements (VDREs), such as an agonist or antagonist activity with regard to receptors of vitamin D or its derivatives. These compounds are not generally natural metabolites of vitamin D. The compounds in question are, in particular, synthetic compounds comprising the vitamin D skeleton with modifications on the side chains and/or likewise

comprising modifications within the skeleton itself. Vitamin D derivatives useful according to the invention thus comprise structural analogues: biaromatics, for example.

By way of illustration of vitamin D derivatives mention may be made in particular of calcipotriol, calcitriol or 1,25-dihydroxyvitamin D_3, doxercalciferol, secalcitol, maxacalcitol, seocalcitol, tacalcitol, paricalcitol, falecalcitriol, 1α,24S-dihydroxyvitamin D2, 1(S),3(R)-dihydroxy-20(R)-[((3-(2-hydroxy-2-propyl)phenyl)methoxy)methyl]-9,10-secopregna-5(Z),7(E),10(19)-triene and mixtures thereof.

According to one preferred embodiment of the invention the vitamin D derivative is calcitriol.

As vitamin D derivatives which can be used according to the invention mention may also be made of the derivatives described in WO 02/34235, WO 00/64450, EP1124779, EP1235824, EP1235777, WO 02/94754, WO 03/050067 and WO 00/26167. The compounds described in WO 00/26167 concern structural analogues of vitamin D which exhibit selective activity on proliferation and on cell differentiation without exhibiting any hypercalcemic character.

Advantageously the amount of vitamin D or vitamin D derivative in solubilized form in the composition of the invention is from 0.00001 to 5% by

weight relative to the total weight of the composition, preferably from 0.0001 to 3% by weight and more particularly from 0.0003 to 1% by weight.

By corticosteroid is meant for the purposes of the present invention a topical steroid from group I, II, III or IV (strong and weak).

According to one advantageous embodiment of the invention the corticosteroid is selected from the group consisting of betamethasone, clobetasol, clobetasone, desoxymethasone, diflucortolone, diflorasone, fluocinonide, flumethasone, fluocinolone, fluticasone, fluprednidene, halcinonide, hydrocortisone, momethasone, triamcinolone and their pharmaceutically acceptable esters and acetonides and mixtures thereof.

As examples of esters or acetonides mention may be made of those selected from the group consisting of the 17-valerate, 17-propionate, 17,21-dipropionate, acetonide, acetonide-21-N-benzoyl-2-methyl-β-alaninate, acetonide-21-(3,3-dimethylbutyrate) and 17-butyrate.

According to one preferred embodiment of the invention the corticosteroid is clobetasol 17-propionate.

Advantageously the amount of corticosteroid in solubilized form in the composition of the invention is from 0.00005 to 3% by weight relative to the total weight of the composition, preferably from 0.0001 to 1%

by weight, and more particularly from 0.001 to 0.1% by weight.

According to one advantageous embodiment of the invention the active principles are solubilized in the same solvent or in two or more solvents.

The solvent of the present invention is selected from pharmaceutically acceptable compounds, which is to say compounds whose use is compatible in particular with application to the skin, the mucosae and/or the keratin fibres. The solvent is generally fluid, and in particular liquid, at ambient temperature and atmospheric pressure.

As solvents according to the invention mention may be made in particular of the following:

- linear or branched aliphatic alcohols having 1 to 6 carbon atoms such as ethanol, isopropanol, butanol and mixtures thereof; preferably the solvent is ethanol;
- oils such as caprylic and capric triglycerides (Miglyol 812), cetearyl isononanoate (Cetiol SN), vegetable oils such as sweet almond oil, sesame oil, wheatgerm oil, olive oil and mixtures thereof;

and mixtures thereof.

As a suitable solvent in the compositions of the invention mention may also be made of:

- compounds of general formula

$R^3(OCH_2C(R^1)H)_xOR^2$, in which x is an integer ranging from 2 to 60, R^1 in each of the x units is independently H or CH_3, R^2 is a linear or branched C_{1-20} alkyl or a benzoyl radical and R^3 is H or a phenylcarbonyloxy radical,

- C_{4-8} dicarboxylic acid di(linear or branched C_{4-10} alkyl) esters, and
- linear or branched C_{12-18} alkyl benzoates.

It will be appreciated that the selection of the solvent depends in particular on the active principle to be solubilized. According to one preferred embodiment of the invention, when the active principles are calcitriol and clobetasol 17-propionate, the solvent is more particularly absolute ethanol.

The solvent is generally present in the compositions of the invention in an amount which is on the one hand sufficient to provide the required solubility of the active principles to be formulated and which on the other hand is compatible with the need to preserve prolonged chemical stability of these active principles. In other words the solvent must be chemically inert towards the active principles.

Advantageously the amount of solvent in a composition of the invention is from 1 to 50% by weight relative to the total weight of the composition, preferably from 2 to 40% by weight and more particularly from 5 to 20% by weight.

The solvent likewise confers a beneficial

effect on the skin penetration rate of the active principles.

Moreover the solvent may also be useful for promoting the compatibility of the silicone agent with one or more other components present in the composition.

According to the invention, one or more cosolvents may be added to the composition. The following non-comprehensive list describes examples of cosolvents which may potentially be used according to the invention:

Commercial name	Chemical name
PROPYLENE GLYCOL	PROPANE-DIOL 1,2
TRANSCUTOL HP	DIETHYLENE GLYCOL MONOETHYL ETHER
PEG 400	MACROGOL 400
PHARMASOLVE	N METHYL 2 PYRROLIDONE
TWEEN 80	POLYSORBATE 80
AUSTRALIAN TEA TREE OIL	MELALEUCA ALTERNIFOLIA
PLUROL DIISOTEARIQUE	TRIGLYCEROL DIISOSTEARATE
BENZYL ALCOHOL	BENZYLIC ALCOHOL
PHENOXYETHANOL	PHENOXYETHANOL
ISOPROPANOL	PROPANOL-2
CRODAMOL DA	DIISOPROPYL ADIPATE
EUTANOL V-PH	OLEYL ALCOHOL

HEXYLENE GLYCOL	METHYL-2-PENTANEDIOL-1,2
PHENYL ETHYL ALCOHOL	2-PHENYLETHANOL
HYDROLITE-5	PENTYLENE GLYCOL
ARLASOLVE DMI	DIMETHYL ISOSORBIDE
SOLUTOL HS-15	MACROGOL-15-HYDROXYSTEARATE

Preferably, these cosolvents will be used in combination with ethanol.

According to the invention the silicone agent comprises at least one organopolysiloxane elastomer.

By organopolysiloxane elastomer is meant any chemically crosslinked siloxane polymer which exhibits viscoelastic properties.

By viscoelastic properties is meant the capability of the elastomer to deform up to a certain point, when subjected to mechanical loading, and to regain its original shape following removal of the said loading.

According to one particular embodiment of the invention the organopolysiloxane elastomer is formulated in a vehicle comprising at least one volatile silicone oil.

By a volatile silicone oil is meant any silicone oil capable of evaporating on contact with the skin, the mucosae or the keratin fibres in less than one hour at ambient temperature and atmospheric pressure.

As examples of volatile silicone oils mention may be made, for example, of linear or cyclic polyorganosiloxane oils having in particular 2 to 10 silicon atoms and optionally containing alkyl or alkoxy groups having 1 to 22 carbon atoms. These silicone oils exhibit in particular a viscosity of less than or equal to 6 centistokes (6×10^{-6} m^2/s).

The volatile silicone oils include in particular the low molecular weight cyclomethicones and dimethicones or mixtures thereof. In particular the volatile silicone oils are selected from cyclic methyl organopolysiloxanes having ring sizes ranging from 4 to 12, such as octamethylcyclotetrasiloxane and decamethylcyclopentasiloxane. As a volatile silicone oil which can be used in the invention mention may also be made of dodecamethylcyclohexasiloxane, heptamethylhexyltrisiloxane, heptamethyloctyltrisiloxane, hexamethyldisiloxane, octamethyltrisiloxane, decamethyltetrasiloxane, dodecamethylpentasiloxane and mixtures thereof.

As organopolysiloxane elastomers which can be used in the compositions of the invention, mention may be made of those which are described in particular in patents US 4 980 167 and US 4 742 142. The compounds in question may in particular be compounds resulting from addition reactions, i.e. products of hydrosilylation or products of polymerization obtained from the addition

of an organopolysiloxane having unsaturated groups such as vinyl or allyl groups, linked in particular to at least one terminal Si atom, and another silicone compound capable of participating in the addition reaction, such as an organohydropolysiloxane.

Mention may in particular be made of silicone elastomers such as those prepared by crosslinking reaction between polysiloxanes (A) containing ≡Si-H groups as defined below, an alpha,omega-diene (B) in the presence of a catalyst and a low molecular weight cyclic or linear polysiloxane (C).

The polysiloxane (A) containing the ≡Si-H unit may be represented by compounds of formula $R^{14}{}_3SiO(R^{15}{}_2SiO)_a(R^{16}HSiO)_bSiR^{14}{}_3$, denoted here as type A^1, and the compounds of formula $HR^{14}{}_2SiO(R^{15}{}_2SiO)_cSiR^{14}{}_2H$ or of formula $HR^{14}{}_2SiO(R^{15}{}_2SiO)_a(R^{16}HSiO)_bSiR^{14}{}_2H$, denoted here as type A^2. In these formulae R^{14}, R^{15} and R^{16} are alkyl groups having one to six carbon atoms, a is an integer varying from 0 to 250, b is an integer varying from 1 to 250 and c is an integer varying from 0 to 250. The molar ratio of the compounds, A^2:A^1, is from 0 to 20, in particular from 0 to 5.

The alpha,omega-diene (B) is a compound of formula $CH_2=CH(CH_2)_dCH=CH_2$ in which d is an integer varying from 1 to 20. Representative examples of appropriate alpha,omega-dienes are 1,4-pentadiene, 1,5-hexadiene, 1,6-heptadiene, 1,7-octadiene, 1,8-nona-

diene, 1,9-decadiene, 1,11-dodecadiene, 1,13-tetradecadiene, and 1,19-eicosadiene.

The expression "low molecular weight polysiloxane (C)" encompasses:

- linear, cyclic or branched volatile methylsiloxanes of low molecular weight,
- linear or cyclic, volatile or non-volatile alkyl- and arylsiloxanes of low molecular weight, and
- linear or cyclic functional siloxanes of low molecular weight.

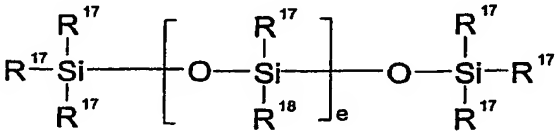
Advantageously the oil (C) is selected from linear or cyclic volatile methylsiloxanes of low molecular weight.

As linear volatile methylsiloxanes mention may be made of hexamethyldisiloxane, octamethyltrisiloxane, decamethyltetrasiloxane, dodecamethylpentasiloxane, tetradecamethylhexasiloxane and hexadecamethylheptasiloxane.

As cyclic volatile methylsiloxanes mention may be made of hexamethylcyclotrisiloxane, octamethylcyclotetrasiloxane, decamethylcyclopentasiloxane and dodecamethylcyclohexasiloxane.

As branched volatile methylsiloxanes mention may be made in particular of heptamethyl-3-[(trimethylsilyl)oxy]trisiloxane, hexamethyl-3,3-bis[(trimethylsilyl)oxy]trisiloxane, and pentamethyl[(trimethylsilyl)oxy]cyclotrisiloxane.

Likewise suitable as compounds (C) in the present invention are non-volatile, low molecular weight polysiloxanes of the general formula:



in which:

- e is such that the polymers conforming to this formula exhibit a viscosity in the range of approximately 100 to 1000 centistokes (mm^2/sec), and is selected in particular from the range from 80 to 375,
- R^{17} and R^{18} are alkyl radicals having 1 to 20 carbon atoms or an aryl group such as a phenyl group.

Among these polysiloxanes mention may be made in particular of polydimethylsiloxane, polydiethylsiloxane, polymethylethylsiloxane, polymethylphenylsiloxane and polydiphenylsiloxane.

Functionalized polysiloxanes of low molecular weight may be represented by fluid siloxanes which carry acrylamide, acrylate, amide, amino, carbinol, carboxyl, chloroalkyl, epoxy, glycol, ketal, mercapto, methyl ester, perfluoro and silanol functions.

Examples of elastomers thus obtained are described in particular in patent US 5,654,362.

Preferably, the silicone elastomer used in the compositions of the invention is in particular of ST Elastomer 10® from Dow Corning, which is a silicone

elastomer formulated in a decamethylcyclopentasiloxane oil, in the form of a thick, translucent gel.

This type of elastomer is synthesized by a crosslinking reaction similar to that described above; that is, it is prepared by a crosslinking reaction between polysiloxanes (A) containing ≡Si-H groups as defined above, an alpha,omega-diene (B) in the presence of a catalyst, and a linear or cyclic polysiloxane of low molecular weight (C), to which vinylsiloxanes (or vinylsilanes) (A') containing $-CH=CH_2$ vinyl groups are added.

The reason for this is that it has been demonstrated that the addition of these vinylsiloxanes (or vinylsilanes) blocks the remaining SiH functions which have not reacted ("quenching agent"). The compounds (A') which can be used for preparing the preferred silicone agents according to the invention are of the type described in US application 5,929,164. Examples of such vinylsiloxane or vinylsilane compounds (A') include vinyl-t-butyldimethylsilane, vinyldiethylmethylsilane, vinylethyldimethylsilane, vinyltriethylsilane, vinyltrimethylsilane, divinyldimethylsilane, divinyltetramethyldisilane, vinylpentamethyldisiloxane, 1,3-divinyltetramethyldisiloxane, a vinyltrisiloxane of structure $(CH_3)_3SiOSi(CH=CH_2)(CH_3)OSi(CH_3)_3$, 1,5-divinylhexamethyltrisiloxane, and a divinylsiloxane oligomer having a $(CH_2=CH)Me_2SiO(Me_2SiO)_8SiMe_2(CH=CH_2)$

structure.

The preferred alpha,omega-diene(B) according to the invention is 1,5-hexadiene.

According to one particular embodiment the silicone agents according to the invention are preferably polysiloxane elastomers which did not contain a hydrophilic group. By a hydrophilic group, according to the invention, is meant, for example, a group of polyoxyalkylene type or a group of glycol type.

The above-defined silicone elastomer may fulfil in particular the function of a thickener in the compositions according to the invention. It may further be involved in stabilizing the said compositions.

Likewise suitable as silicone elastomers in accordance with the invention are silicone polymers having an average molecular weight of at least 10 000 (for example ranging from 10 000 to 10 000 000). Examples of silicone polymers include crosslinked siloxane copolymers, for example copolymers of dimethicone or dimethicone derivatives, such as the stearylmethyl-dimethylsiloxane copolymer (Gransil SR-CYC® from the company Grant Industries), Polysilicone-11® (i.e. a crosslinked silicone elastomer formed by reacting vinyl-terminated silicone and methylhydro-dimethylsiloxane in the presence of cyclomethicone), crosslinked cetearyldimethicone/vinyldimethicone

copolymers (i.e. a cetearyldimethicone copolymer crosslinked with a vinyldimethylpolysiloxane), a crosslinked dimethicone/phenylvinyldimethicone polymer (i.e. a dimethylpolysiloxane copolymer crosslinked with phenylvinyldimethylsiloxane), and a crosslinked dimethicone/vinyldimethicone copolymer (i.e. a dimethylpolysiloxane copolymer crosslinked with vinyldimethylsiloxane).

Silicone gels of this kind may be obtained commercially in particular from Grant Industries. Examples of such gels include the mixture of cyclomethicone and polysilicone-11 sold for example under the name Gransil GCM5®, the mixture of cyclotetrasiloxane and polysilicone-11 sold for example under the name Gransil PS-4®, the mixture of cyclopentasiloxane and polysilicone-11 sold for example under the name Gransil PS-5®, the mixture of cyclopentasiloxane, dimethicone and polysilicone-11 sold for example under the name Gransil DMCM-5®, the mixture of cyclotetrasiloxane, dimethicone and polysilicone-11 sold for example under the name Gransil DMCM-4®, the mixture of polysilicone-11 and isododecane sold for example under the name Gransil IDS®, and the mixture of cyclomethicone, polysilicone-11 and phytosphingosine sold for example under the name Gransil SPH®. Examples of gels available from the company General Electric include in particular a crosslinked polymer called

cyclopentasiloxane and dimethicone/vinyldimethicone crosspolymer SFE839®.

Other silicone gels may also be obtained commercially in particular from Shin-Etsu under the following references: KSG-15, KSG-16 and KSG-17, and KSG-21.

Advantageously the amount of silicone agent in a composition of the invention is from 20 to 95% by weight relative to the total weight of the composition, preferably from 20 to 90% by weight.

The amount of silicone agent in a composition of the invention may vary substantially, in particular depending on the viscosity of the desired composition.

Advantageously the amount of organopolysiloxane elastomer in a composition of the invention is from 5 to 80% by weight relative to the total weight of the composition, preferably from 10 to 40% by weight.

As indicated above, the preferred silicone agent is "ST Elastomer 10®" from Dow Corning, a commercial product composed of an organopolysiloxane elastomer present at a concentration of 12% in a decamethylcyclopentasiloxane oil (approximately 85%).

The composition according to the invention may further comprise various other ingredients. The selection of these supplementary ingredients, like that of their respective amounts, is made so as not to do detriment to the expected properties of the

composition. In other words these compounds must not adversely affect the chemical stability of the active principles or their solubility.

According to one advantageous embodiment of the invention the composition further comprises an antioxidant selected from the group consisting of butylated hydroxytoluene (BHT), butylated hydroxy-anisole (BHA), DL-alpha-tocopherol, superoxide dismutase, ubiquinol or certain chelating agents such as disodium edetate.

According to another advantageous embodiment the composition further comprises an oily additive selected from the group consisting of isopropyl palmitate, dicaprylyl ether, dimethicone or mixtures thereof.

In the compositions of the invention the addition of an oily additive makes it possible to avoid fluffing and to have a light, more substantive residue from the standpoint of the treatment of psoriasis.

The composition of the invention may further comprise one or more pharmaceutical excipients suitable for topical application.

By way of examples of pharmaceutical excipients suitable for topical application mention may be made of:

- wetting agents;
- flavour enhancers;

- stabilizers;
- moisture regulators;
- pH regulators;
- osmotic pressure modifiers;
- emulsifiers;
- UV-A and UV-B filters;
- penetration promoters;
- and synthetic polymers.

As will be appreciated, the person skilled in the art will ensure that any compound or compounds to be added to these compositions will be selected such that the advantageous properties intrinsically attached to the present invention are not, or not substantially, adversely affected by the intended addition.

According to one advantageous embodiment of the invention the composition is in the form of an ointment, gel, cream or unguent.

Preferably the compositions of the invention are in the form of an ointment. For the purposes of the present invention and in accordance with the U.S. Pharmacopeia (USP) an ointment is a semisolid preparation intended for external application to the skin or mucosae. Ointments or unguents are used topically for numerous applications, for example as barrier creams, antiseptic creams, emollient creams, etc. Ointments are used for their emollient effect; they are simple to apply and readily penetrate the

skin.

Advantageously the compositions according to the invention prove, following application, to be exempt from effects of stickiness, greasiness and shine and instead to provide a soft feel. This new type of ointment enhances absorption through the skin, leaves a non-greasy powdery residue and provides ease of application, allowing improvement in the adherence by the patient to his or her treatment. Moreover, one advantageous aspect of this composition is the absence of preservative.

Additionally the inventive compositions show themselves to be particularly effective for preserving satisfactory chemical stability of the active principles which are sensitive to oxidation, to water and to aqueous environments in general. The term "satisfactory chemical stability" applies to a composition which, over a period of at least three months, respectively at ambient temperature and at 40°C:

- does not present any substantial modification of its macroscopic appearance,
- has an active principles content of at least 80%, in particular at least 90% and more particularly at least 95% of the initial weight content.

The present invention likewise pertains to the use of a silicone agent comprising at least one

organopolysiloxane elastomer for preparing an anhydrous pharmaceutical composition intended for the treatment of psoriasis, the said composition comprising as active principles vitamin D or a vitamin D derivative and a corticosteroid, the said active principles each being in a solubilized form.

In the abovementioned use the pharmaceutical composition is as defined above.

According to one advantageous embodiment of the invention the composition is prepared cold, in other words at ambient temperature between 20°C and 25°C. The composition is prepared by mixing at least two distinct phases: a phase comprising at least the silicone agent and a phase comprising at least the active principles and the solvent or solvents of the said active principles.

The examples below illustrate the invention; they do not limit it in any way whatsoever.

Example 1: Solubility and stability tests on the active principles

The stability of calcitriol was tested in various solvents, including ethanol 100 and a 75%/25% ethanol 100/cyclomethicone mixture.

a) Stability of calcitriol in ethanol

A 30 ppm solution of calcitriol in absolute ethanol to 100% is prepared in the presence of 0.02% of butylated hydroxytoluene (BHT).

The results of an HPLC assay technique against a reference are indicated in table 1 below.

At the starting time (T0) the calcitriol concentration is taken to be 100%.

Table 1:

Stability conditions	T 1 week	T 2 weeks	T 3 weeks	T 4 weeks
-18°C	100.9%	100.5%	99.5%	99.5%
+4°C	97.7%	98.6%	98.1%	97.7%
+30°C	/	93.4%	/	93.0%

b) Stability of calcitriol in the (ethanol/cyclopentasiloxane) mixture

A 30 ppm solution of calcitriol in absolute ethanol to 100% is prepared in the presence of 0.02% of BHT.

The results of an HPLC assay technique against a reference are indicated in table 2 below.

At the starting time (T0) the calcitriol concentration is taken to be 100%.

Table 2:

Stability conditions	T 2 weeks	T 3 weeks	T 4 weeks
-18°C	100.4%	101.3%	99.2%
+4°C	99.2%	99.6%	97.5%
+30°C	93.8%	/	93.3%

Example 2: Preparation of a composition of the invention

The process described below is a general process for preparing a silicone ointment comprising a vitamin D derivative and a corticosteroid. The process is carried out at ambient temperature, between 20°C and 25°C.

a) First step: Preparation of the phase comprising the silicone agent (phase A)

The constituents of phase A are weighed out into a beaker: Elastomer ST 10®, silicone oil and oily additive.

These constituents are homogenized until a homogeneous gel is obtained.

b) Second step: Preparation of the phase comprising the active principles (phase B)

A stock solution is prepared which comprises a vitamin D derivative in an appropriate solvent and an antioxidant. The solution is stirred until the active dissolves.

The corticosteroid is weighed out and placed in its solvent. The solution is stirred until the active dissolves.

The two active phases are incorporated into phase A with stirring. The mixture is homogenized.

When the solvent is the same for both active principles, the corticosteroid is added to the stock solution of the vitamin D derivative.

Example 3: Example of a pharmaceutical composition of the invention

(1) composition

Composition 1	
Ingredients	Amounts in % weight per weight
ISOPROPYL PALMITATE (oily additive)	1

CYCLOPENTASILOXANE (oil)	16
CYCLOMETHICONE 5/ DIMETHICONE CROSSPOLYMER (silicone agent)	74.9347
BUTYLATED HYDROXYTOLUENE (antioxidant)	0.04
CALCITRIOL (active)	0.0003
CLOBETASOL PROPIONATE (active)	0.025
ABSOLUTE ETHANOL (solvent)	8

(2) Physical stability

The physical stability of the compositions is measured by macroscopic and microscopic observation of the composition at ambient temperature, at 4°C and at 40°C after 15 days, 1 month, 2 months and 3 months.

Conclusion:

At ambient temperature the macroscopic observation makes it possible to ensure the physical integrity of the compositions and the microscopic observation makes it possible to verify that there is no recrystallization of the solubilized active principles.

At 4°C the microscopic observation verifies the non-recrystallization of the solubilized active principles.

At 40°C the macroscopic observation verifies the integrity of the final composition.

Characterization of the final composition is completed with a measurement of the flow point. A Haake rheometer of type VT550 is used with a SVDIN measuring spindle. The rheograms are performed at 25°C and at a shear rate of 4 s^{-1} (γ), measuring the shearing stress. By flow point ($\tau 0$ expressed in pascals) is meant the force required (minimum shearing stress) to overcome the van der Waals cohesion forces and bring about the flow. The flow point is taken to be the value found at a shear rate of 4 s^{-1}.

These measurements are carried out at T0 and after 1, 2 and 3 months.

These measurement techniques show that the composition of the invention is stable at least for 1 month at 4°C and 40°C.

Specifications at T0

Opalescent colourless flexible ointment

Time→ Stability conditions↓	T 1M	T 2M	T 3M
AT	Complies with specifications	Complies with specifications	Complies with specifications
+4°C	Complies with specifications	Complies with specifications	Complies with specifications
+40°C	Complies with specifications	Complies with specifications	Complies with specifications

(3) Chemical stability of the actives within the composition

Stability of calcitriol

The active is assayed by external calibration in HPLC.

Time→ Stability conditions↓	T0	T 15 days	T 1M	T 2M
AT	102.2%	100.7%	101.7%	103.3%
+40°C		109.8%	111.0%	103.6%

Stability of clobetasol 17-propionate

Assay of the active by internal calibration in HPLC.

Time→ Stability conditions↓	T0	T 15 days	T 1M	T 2M
AT	103.2%	101.6%	101.0%	103.0%
+40°C		106.4%	108.6%	111.4%

Example 4: Example of a pharmaceutical composition of the invention

Composition 2	
Ingredients	Amounts in % weight per weight
DICAPRYLYL ETHER (oily additive)	15
BUTYLATED HYDROXYTOLUENE (antioxidant)	0.04
CALCITRIOL (active)	0.0003
CYCLOPENTASILOXANE (oil)	8
CYCLOMETHICONE 5 / DIMETHICONE CROSSPOLYMER (silicone agent)	75.935
CLOBETASOL PROPIONATE (active)	0.025
ABSOLUTE ETHANOL (solvent)	1

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The physical stability of the compositions is measured as described above. The conclusions are identical with what was described before.

Example 5: Example of a pharmaceutical composition of the invention

Composition 3	
Ingredients	Amounts in % weight per weight
DIMETHICONE 200-350cSt	1
CYCLOPENTASILOXANE	12
CYCLOMETHICONE 5/ DIMETHICONE CROSSPOLYMER	qs 100
BUTYLATED HYDROXYTOLUENE	0.04
CALCITRIOL	0.0003
CLOBETASOL PROPIONATE	0.025
ABSOLUTE ETHANOL	8

The physical stability of the compositions is measured as described above. The conclusions are identical with what was described before.

Example 6: Example of a pharmaceutical composition of the invention

CONSTITUENTS	%
ISOPROPYL PALMITATE	1
CYCLOPENTASILOXANE	12
CYCLOMETHICONE 5/DIMETHICONE CROSS POLYMER	QS 100
BUTYLATED HYDROXYTOLUENE	0.04
CALCITRIOL	0.0003
CLOBETASOL 17-PROPIONATE	0.025
ABSOLUTE ETHANOL	6

a) physical stability of the composition

Time→ Stability conditions↓	T 1M	T 2M	T 3M
AT	Complies with specifications	Complies with specifications	Complies with specifications
+4°C	Complies with specifications	Complies with specifications	Complies with specifications
+40°C	Complies with specifications	Complies with specifications	Complies with specifications

(b) Chemical stability of the actives within the composition

Stability of calcitriol

Time→ Stability conditions↓	T0	T 1M	T 2M	T 3M
AT	115.4%	115%	115.2%	119.2%
+40°C		111.9%	119.7%	119.5%

Stability of clobetasol 17-propionate

Time→ Stability conditions↓	T0	T 1M	T 2M	T 3M
AT	98.0%	99.2%	97.1%	99.6%
+40°C		98.1%	100.2%	98.9%

Example 7: Example of a pharmaceutical composition of the invention

CONSTITUENTS	%
N-Methyl-2-pyrrolidone	0.80
CYCLOPENTASILOXANE	9
CYCLOMETHICONE 5/DIMETHICONE CROSS POLYMER	QS 100
BUTYLATED HYDROXYTOLUENE	0.04
CALCITRIOL	0.0003
CLOBETASOL 17-PROPIONATE	0.05
ABSOLUTE ETHANOL	6

a) physical stability of the composition

Time→ Stability conditions↓	T 1M	T 2M
AT	Complies with specifications	Complies with specifications
+4°C	Complies with specifications	Complies with specifications
+40°C	Complies with specifications	Complies with specifications

(b) Chemical stability of the actives of the composition

Stability of calcitriol

Time→ Stability conditions↓	T0	T 1M	T 2M
AT	104.1%	107.6%	102.9%
+40°C		103.1%	103.3%

Stability of clobetasol 17-propionate

Time→ Stability conditions↓	T0	T 1M	T 2M
AT	98.4%	102.7%	100.4
+40°C		101.0%	100.0

Example 8: Example of a pharmaceutical composition of the invention

CONSTITUENTS	%
PEG 400	1.00
CYCLOPENTASILOXANE	9
CYCLOMETHICONE 5/DIMETHICONE CROSS POLYMER	QS 100
BUTYLATED HYDROXYTOLUENE	0.04
CALCITRIOL	0.0003
CLOBETASOL 17-PROPIONATE	0.05
ABSOLUTE ETHANOL	6

a) physical stability of the composition

Time→ Stability conditions↓	T 1M	T 2M
AT	Complies with specifications	Complies with specifications

+4°C	Complies with specifications	Complies with specifications
+40°C	Complies with specifications	Complies with specifications

(b) Chemical stability of the actives within the composition

Stability of calcitriol

Time→ Stability conditions↓	T0	T 1M	T 2M
AT	106.4%	103.3%	105.2%
+40°C		101%	102.8%

Stability of clobetasol 17-propionate

Time→ Stability conditions↓	T0	T 1M	T 2M
AT	102.8%	98.6%	99.6%
+40°C		97.5%	92.3%

Example 9: Study of the release/penetration *in vitro* on human skin of the active clobetasol 17-propionate contained in 3 different formulations, including one according to the invention

The objective is to quantify the skin penetration of the formulated active in different formulations *in vitro* on human skin after 16 hours of application.

Formulations tested:

- Temovate® emollient cream containing 0.05% (w/w) of clobetasol 17-propionate
- Temovate® cream containing 0.05% (w/w) of clobetasol 17-propionate
- Composition according to the invention of formula A below:

Ingredients	Amounts in % weight per weight
ISOPROPYL PALMITATE (oily additive)	1
CYCLOPENTASILOXANE (oil)	16
CYCLOMETHICONE 5/ DIMETHICONE CROSSPOLYMER (silicone agent)	74.9347
BUTYLATED HYDROXYTOLUENE (antioxidant)	0.04
CALCITRIOL (active)	0.0003

CLOBETASOL PROPIONATE (active)	0.025
ABSOLUTE ETHANOL (solvent)	8

The Temovate® creams are sold by the company Glaxo Smith Kline.

Experimental conditions: The percutaneous absorption is evaluated by means of diffusion cells consisting of 2 compartments separated by human skin. The formulations were applied without occlusion for an application time of 16 hours. The formulations were applied at a rate of 10 mg of formulation per cm^2 (*i.e.* 10 micrograms of clobetasol 17-propionate). Throughout the study, the dermis is in contact with a receiving liquid which is not renewed as a function of time (static mode). The experiments were conducted with 3 samples of skin originating from 3 different donors. At the end of the application period, the surface excess is removed and the distribution of the clobetasol 17-propionate is quantified in the different compartments of the skin and in the receiving liquid. The concentrations of clobetasol 17-propionate were quantified using a HPLC/MS/MS method which is conventionally known to the skilled person. (LQ: 1 $ng.ml^{-1}$).

The results are expressed as a % of the applied dose (mean +/- standard deviation) and are set out in the table below.

Formulation		**Total amount having penetrated**
Emollient Temovate cream	Mean	**5.00**
	SEM	**1.34**
Temovate cream	Mean	**8.43**
	SEM	**0.79**
Composition A	Mean	**9.96**
	SEM	**1.36**

The results show that the amount of clobetasol having penetrated with the composition according to the invention is equivalent to that of the Temovate cream.

CLAIMS

1. Anhydrous pharmaceutical composition intended for the treatment of psoriasis, characterized in that it comprises a silicone agent comprising at least one organopolysiloxane elastomer, a compound A selected from vitamin D or a vitamin D derivative and a compound B selected from a corticosteroid, the said compounds A and B each being in a solubilized form in the said composition.

2. Pharmaceutical composition according to Claim 1, characterized in that the difference in optimum pH stability of the compound A and the optimum pH stability of the compound B is at least 1.

3. Composition according to either of Claims 1 and 2, characterized in that the vitamin D derivative is selected from the group consisting of calcipotriol, calcitriol or 1,25-dihydroxyvitamin D_3, doxercalciferol, secalcitol, maxacalcitol, seocalcitol, tacalcitol, paricalcitol, falecalcitriol, 1α,24S-dihydroxyvitamin D2, 1(S),3(R)-dihydroxy-20(R)-[((3-(2-hydroxy-2-propyl)phenyl)methoxy)methyl]-9,10-secopregna-5(Z),7(E),10(19)-triene and mixtures thereof.

4. Composition according to Claim 3, characterized in that the vitamin D derivative is calcitriol.

5. Composition according to any one of Claims 1

to 4, characterized in that the corticosteroid is selected from the group consisting of betamethasone, clobetasol, clobetasone, desoxymethasone, diflucortolone, diflorasone, fluocinonide, flumethasone, fluocinolone, fluticasone, fluprednidene, halcinonide, hydrocortisone, momethasone, triamcinolone and their pharmaceutically acceptable esters and acetonides and mixtures thereof.

6. Composition according to Claim 5, characterized in that the esters or acetonides are selected from the group consisting of 17-valerate, 17-propionate, 17,21-dipropionate, acetonide, acetonide-21-N-benzoyl-2-methyl-β-alaninate, acetonide-21-(3,3-dimethylbutyrate) and 17-butyrate.

7. Composition according to either of Claims 5 and 6, characterized in that the corticosteroid is clobetasol 17-propionate.

8. Composition according to any one of Claims 1 to 7, characterized in that the compounds A and B are solubilized in the same solvent or in two or more solvents.

9. Composition according to any one of Claims 1 to 8, characterized in that it is intended for topical application.

10. Composition according to any one of Claims 1 to 9, characterized in that it has a water content of less than or equal to 5% by weight relative to the

total weight of the composition, in particular less than or equal to 3%, and especially zero.

11. Composition according to Claim 8, characterized in that the solvent is selected from the group consisting of:

- aliphatic alcohols having 1 to 6 carbon atoms such as ethanol, isopropanol, butanol and mixtures thereof;
- oils such as caprylic and capric triglycerides, cetearyl isononanoate, vegetable oils such as sweet almond oil, sesame oil, wheatgerm oil, olive oil and mixtures thereof;

and mixtures thereof.

12. Composition according to Claim 11, characterized in that the solvent is ethanol.

13. Composition according to any one of Claims 1 to 12, characterized in that the organopolysiloxane elastomer is formulated in at least one volatile silicone oil selected from linear or cyclic polyorganosiloxane oils having 2 to 10 silicon atoms and optionally containing alkyl or alkoxy groups of 1 to 22 carbon atoms.

14. Composition according to any one of Claims 1 to 13, characterized in that the amount of silicone agent is from 20 to 90% by weight relative to the total weight of the composition, preferably from 30 to 80% by weight.

15. Composition according to any one of Claims 1 to 14, characterized in that the amount of organopolysiloxane elastomer is from 20 to 90% by weight relative to the total weight of the composition, preferably from 30 to 80% by weight.

16. Composition according to any one of Claims 1 to 15, characterized in that the amount of vitamin D or vitamin D derivative in solubilized form is from 0.00001 to 5% by weight relative to the total weight of the composition.

17. Composition according to any one of Claims 1 to 16, characterized in that the amount of vitamin D or vitamin D derivative in solubilized form is from 0.0001 to 3% by weight.

18. Composition according to any one of Claims 1 to 17, characterized in that the amount of vitamin D or vitamin D derivative in solubilized form is from 0.0003 to 1% by weight.

19. Composition according to any one of Claims 1 to 18, characterized in that the amount of corticosteroid in solubilized form is from 0.00005 to 3% by weight relative to the total weight of the composition.

20. Composition according to any one of Claims 1 to 19, characterized in that the amount of corticosteroid in solubilized form is from 0.0001 to 1% by weight.

21. Composition according to any one of Claims 1 to 20, characterized in that the amount of corticosteroid in solubilized form is from 0.001 to 0.1% by weight.

22. Composition according to any one of Claims 8 to 21, characterized in that the amount of solvent is from 1 to 50% by weight relative to the total weight of the composition, preferably from 2 to 40% by weight and more particularly from 5 to 20% by weight.

23. Composition according to any one of Claims 1 to 22, characterized in that it further comprises an antioxidant selected from the group consisting of butylated hydroxytoluene (BHT), butylated hydroxy-anisole (BHA), DL-alpha-tocopherol, superoxide dismutase, ubiquinol or certain chelating agents.

24. Composition according to any one of Claims 1 to 23, characterized in that it further comprises an oily additive selected from the group consisting of isopropyl palmitate, dicaprylyl ether, dimethicone or mixtures thereof.

25. Composition according to any one of Claims 1 to 24, characterized in that it comprises one or more pharmaceutical excipients suitable for topical application.

26. Composition according to any one of Claims 1 to 25, characterized in that it is in the form of an ointment, gel, cream or unguent.

27. Use of a silicone agent comprising at least one organopolysiloxane elastomer for preparing an anhydrous pharmaceutical composition intended for the treatment of psoriasis, the said composition comprising as active principles vitamin D or a vitamin D derivative and a corticosteroid, the said active principles each being in a solubilized form.

28. Use according to Claim 27, wherein the composition is as defined in any one of Claims 1 to 26.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/007974

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/573 A61K31/59 A61K31/592 A61K31/593 A61K47/08
A61K47/10 A61K47/14 A61K47/24 A61P17/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	EP 0 998 943 A (PANIN GIORGIO) 10 May 2000 (2000-05-10) page 2, line 40 - page 3, line 12 page 3, exemple	1-28

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 October 2005	03/11/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Albrecht, S

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International Application No
PCT/EP2005/007974

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INTERNATIONAL SEARCH REPORT

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PCT/EP2005/007974

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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